



Human cancer relevant genomic alterations in a population based genetically engineered murine model of human breast cancer

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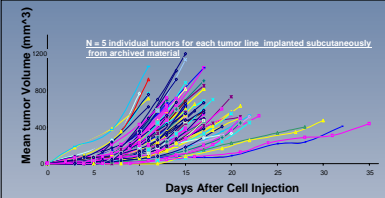
Abstract (#1734)

Traditional preclinical models of human cancer have been of limited utility in guiding clinical development of anti-cancer genetic diversity and variation in response to a given treatment are the potential challenges to any human cancer therapeutic strategies. Mimicking known human cancer relevant mutations and making genetically engineered model of human cancer has, so far been, proven to be useful, but recapitulating the natural diversity of the human cancers at the genetic and drug response level has been challenging. To create a population based model of human HER2 amplified breast cancer, we used novel ES cell based chimeric approach to generate over 100 murine breast adenocarcinomas engineered to combine HER2 overexpression and INK4A/ARF/- knockout. Each of these primary tumors was then propagated in vivo to generate an archive of frozen tumor material suitable for further drug testing and molecular characterization. Tumors from these archives were characterized for phenotypic and molecular variation, and found to show significant variation in various aspects of tumor growth including growth rate, stromal involvement, angiogenesis and microarray profile.

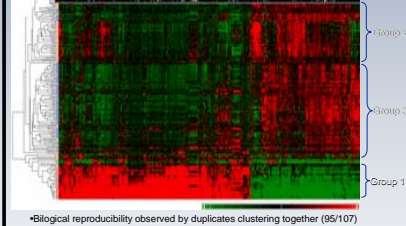
Genomic alterations, especially regional chromosomal amplifications and deletions are hallmarks of solid tumor genome. Array-based comparative genome hybridization (array-CGH) technology was used to characterize these tumors for the presence of DNA alterations. Synthetic to human tumors, the archived population of murine GEM tumors also revealed lower amplitude DNA alterations present in many of these tumors and more focal, larger amplitude alterations that are specific to few tumors. By combining microarray based expression data and aCGH data from same tumors we were able to show co-linear co-expressed overexpression of genes from genomic regions that are either amplified or deleted respectively. Apart from novel regions of focal DNA gains and losses, human cancer relevant genomic alterations that were found in this model include regions surrounding MDM2, CDK4, CDK6, Myc and PTEN. Tumors that showed focal PTEN deletions, when subjected to Rapamycin treatment showed significant tumor growth inhibition raising the possibility that a comprehensive analysis of DNA alterations could potentially be used in predicting drug response.

Human Cancer Relevant Genomic Variations in BH Tumors

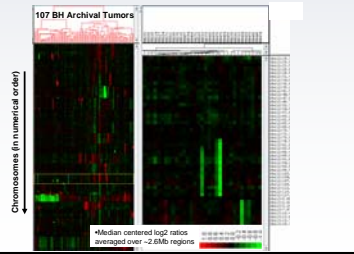
Natural variation in the growth profile of ~107 murine inducible Breast Her2 tumors



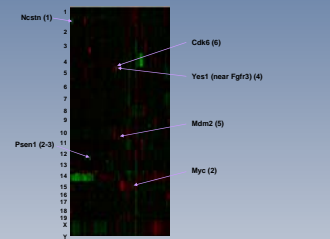
Expression profile analysis using microarray of 107 murine inducible breast Her2 tumors reveal diversity among these tumors



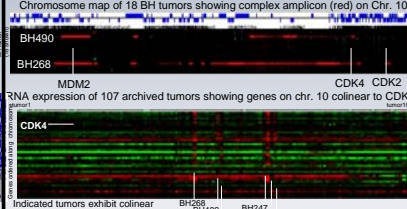
Global view of DNA alterations in various chromosomes from 107 Her2 inducible murine breast tumors



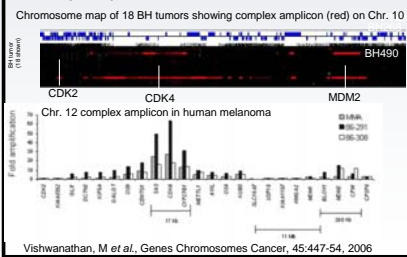
Human cancer relevant genomic amplifications in deletions in archived murine breast tumors



Tumors with focal amplifications show colinear overexpression of genes from the amplicon



Similar complex amplification found in human melanoma and murine BH tumors

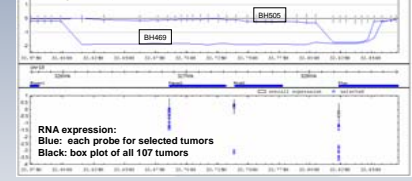


DNA Changes can Predict Drug Response

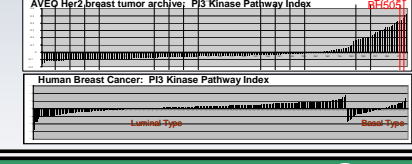
High Resolution aCGH shows chromosomal loss of PTEN in BH tumors



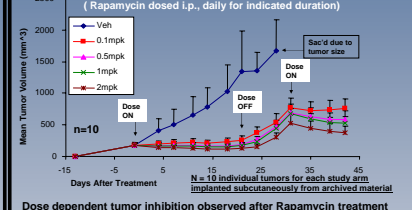
Visualization of magnitude and size of DNA changes with associated gene expression: PTEN Deletion in BH505 and BH469



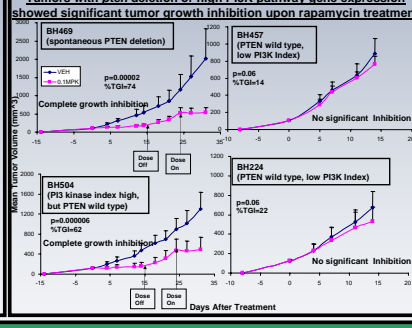
Tumors ranked using expression based PI3K Index (correlates with chromosomal PTEN loss)



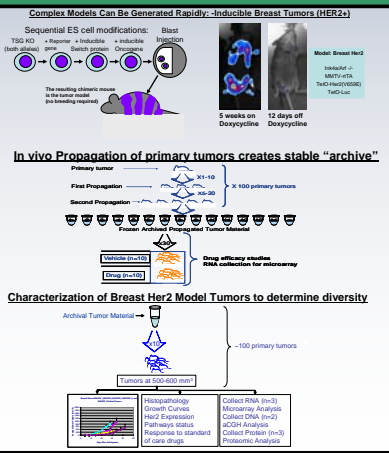
PTEN deleted BH505 tumor showed complete growth inhibition upon 0.1mpk treatment of Rapamycin (Rapamycin dosed i.p., daily for indicated duration)



Tumors with PTEN deletion or high PI3K pathway gene expression showed significant tumor growth inhibition upon rapamycin treatment



Chimeric Inducible Models



Summary

- Array CGH analysis of population of murine inducible tumors showed lower amplitude alterations spanning wider genomic areas and more focal larger amplitude changes. Complex amplicons that were found in human cancer were also seen in the murine BH model.
- Human cancer relevant chromosomal losses and gains (e.g. regions surrounding MDM2, CDK4, CDK6, Myc and PTEN) observed in the archived inducible breast Her2 tumors
- Comparison of tumor specific chromosomal alterations and microarray based gene expression changes reveal colinear co-expression of relevant genes from the affected chromosomal regions in this tumor model
- Tumors with focal PTEN deletion, upon rapamycin treatment showed significant tumor growth inhibition
PI also visit Poster #3615 by Karuppiyah Kannan, Ph.D., Session: Molecular Predictors of Drug Sensitivity and Resistance; Tuesday, April 15th 8AM-12Noon; Exhibit Hall B-F, Section 10, Board#4

Vishwanathan, M et al., Genes Chromosomes Cancer, 45:44-54, 2006